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ETIOLOGY, PREVALENCE, AND DEVELOPMENT OF A NOVEL TREATMENT FOR BODY DYSMORPHIC DISORDER

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ETIOLOGY, PREVALENCE, AND DEVELOPMENT OF A NOVEL TREATMENT FOR BODY DYSMORPHIC DISORDER

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Dedicated to my late father.

ABSTRACT

Body dysmorphic disorder (BDD) is characterized by an intense preoccupation with perceived defects in physical appearance that are not noticeable, or only appear slight to others. While effective treatment for this disorder does exist (e.g. cognitive behavioural therapy; CBT) most sufferers do not get access to it. BDD usually begins during adolescence but few studies have explored the prevalence and pattern of comorbidities in this age group. Moreover, the etiology of dysmorphic concerns in young people is unknown. The aims of this thesis were therefore to develop a novel therapist-guided internet-based CBT program for BDD (BDD-NET), with the intention to increase availability of CBT for BDD, and to conduct a genetic epidemiological study of BDD symptoms in adolescents and young adults.

In Study I, the feasibility of BDD-NET was evaluated in a sample of 23 self-referred adults diagnosed with BDD. Large and significant reductions in BDD symptoms were observed after treatment, and participants deemed the treatment as highly acceptable.

In Study II, the efficacy of BDD-NET was determined in a single-blind randomized controlled trial. Ninety-four participants with BDD were randomized to BDD-NET or online supportive therapy. BDD-NET was superior to supportive therapy, and 39% of those that had received BDD-NET were in remission, compared to 9% in the control group. All participants in the control group were offered BDD-NET after the controlled follow-up.

In Study III, all participants ($n=88$) that had received BDD-NET in Study II were followed-up for 2-years to evaluate the long-term efficacy of BDD-NET. The treatment effects of BDD-NET were sustained in the long-term and at the 2-year follow-up, 56% of participants were in remission.

In Study IV, the prevalence of clinically significant BDD symptoms, and risks for co-existing psychopathology were estimated in three population-based twin cohorts at ages 15 ($n=6,968$), 18 ($n=3,738$), and 20-28 ($n=4,671$). A classical twin design was used to determine the relative contribution of genetic and environmental influences on body dysmorphic concerns in these age groups. The prevalence of BDD was estimated between 1% and 2%. Heritability of dysmorphic concerns was estimated between 37-49%, with the remaining variance explained by non-shared environment. The risks for co-existing psychopathology were elevated, with odds ratios ranging from 2.3-13.2.

In conclusion, BDD-NET is an efficacious treatment for this disorder, both in the short-term and in the long-term, and it has the potential to increase access to evidence based care for people with BDD. BDD symptoms in young people are relatively common, with genetic factors accounting for roughly half of the variation in dysmorphic concerns. The risks for co-existing psychopathology are elevated in young people that screened positive for BDD.

LIST OF SCIENTIFIC PAPERS

- I. Enander J, Ivanov VZ, Andersson, E, Mataix-Cols D, Ljótsson B, Rück C. Therapist-guided, Internet-based cognitive-behavioural therapy for body dysmorphic disorder (BDD-NET): a feasibility study. *BMJ Open* 2014;4:e005923
- II. Enander J, Andersson E, Mataix-Cols D, Lichtenstein L, Alström K, Andersson G, Ljótsson B, Rück C. Therapist guided internet based cognitive behavioural therapy for body dysmorphic disorder: single blind randomised controlled trial. *BMJ* 2016;352:i241.
- III. Enander J, Ljótsson B, Anderhell L, Runeborg M, Flygare O, Cottman O, Andersson E, Dahlén S, Lichtenstein L, Ivanov VZ, Mataix-Cols D, Rück C. Long term outcome of therapist-guided internet-based cognitive behavioural therapy for body dysmorphic disorder (BDD-NET): A naturalistic 2-year follow-up after a randomised controlled trial. *Manuscript*.
- IV. Enander J, Ivanov VZ, Mataix-Cols D, Kuja-Halkola R, Ljótsson B, Lundström S, Pérez-Vigil A, Monzani B, Lichtenstein P, Rück C. Prevalence, and heritability of body dysmorphic symptoms in adolescents and young adults: A population-based nationwide twin study. *Manuscript*.

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LIST OF ABBREVIATIONS

ADHD	Attention deficit/hyperactivity disorder
ASD	Autism spectrum disorder
AUD	Alcohol use disorder
BDD	Body dysmorphic disorder
BDD-NET	Therapist-guided internet-based cognitive behavior therapy for body dysmorphic disorder
BDD-YBOCS	Yale-Brown obsessive compulsive scale modified for body dysmorphic disorder
CATSS	Child and Adolescent Twin Study in Sweden
CBT	Cognitive behavior therapy
CI	Confidence interval
DCQ	Dysmorphic concerns questionnaire
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th Edition
EQ5D	EuroQol EQ5D – health related quality of life scale
GAF	Global assessment of functioning scale
HD	Hoarding disorder
ICBT	Internet based cognitive behavior therapy
ICC	Intraclass correlation
MADRS-S	Montgomery-Åsberg depression rating scale self-report
OCD	Obsessive-compulsive disorder
RCT	Randomized controlled trial
SSRI	Selective serotonin-reuptake inhibitors
YATSS	Young Adult Twins in Sweden Study

1 INTRODUCTION

“The dysmorphophobic, indeed, is a veritably unhappy individual, who in the midst of his daily affairs, in conversations, while reading, at table, in fact anywhere and at any hour of the day, is suddenly overcome by the fear of some deformity that might have developed in his body without his noticing it. He fears having or developing a compressed, flattened forehead, a ridiculous nose, crooked legs, etc., so that he constantly peers in the mirror, feels his forehead, measures the length of his nose, examines the tiniest defects in his skin, or measures the proportions of his trunk and the straightness of his limbs, and only after a certain period of time, having convinced himself that this has not happened, is able to free himself from the state of pain and anguish the attack put in him. But should no mirror be at hand, or should he be prevented from quieting his doubts in some way or other by means of some mechanism or movements of the most outlandish kinds, the attack does not end very quickly, but rather may reach a very painful intensity, even to the point of weeping and desperation.”

Enrico Morselli, 1891.

1.1 BODY DYSMORPHIC DISORDER

Body dysmorphic disorder (BDD) was first described in 1891 by Italian physicist Enrico Morselli who coined the term “dysmorphophobia” – a fear of being or becoming physically deformed.¹ In contemporary psychiatry, the term dysmorphophobia has been replaced with “body dysmorphic disorder” and today it is classified as an “obsessive-compulsive and related disorder” in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).²

Body dissatisfaction is common both among men and women,³ and it is perfectly natural to occasionally brood over one’s appearance from time to time, however, BDD should not be mistaken for normal appearance concerns. An individual suffering from BDD has an *intense* preoccupation with perceived defects in physical appearance that are not noticeable, or only appear slight to others.² Additionally, the preoccupation is markedly *disproportionate*, and thoughts about the disliked body parts are perceived as intrusive, difficult to control and time consuming to the point of becoming an obsession.⁴ In other words, BDD involves a preoccupation with one's appearance that has become severe enough to significantly impair one's life. Moreover, individuals with BDD have a strong belief that they look ugly or abnormal, and usually challenge the idea that beauty is in the eye of the beholder. Roughly two-thirds of individuals with the disorder endorse lifetime delusions or ideas of reference, believing that other people mock them or take special notice of them because of how they look.⁵ Insight that the perceived defects are not real varies on a continuum from fair insight to delusional beliefs, but is typically poor.^{6,7} Another hallmark of BDD is repetitive behaviors (such as compulsive mirror gazing, excessive grooming or camouflaging of disliked body areas) that is performed in an attempt to alleviate the anxiety caused by the distorted body

image.^{2,8} BDD is associated with significant distress, poor quality of life, and psychosocial impairment, with more severe symptoms predicting worse functioning.⁸⁻¹⁰ Some individuals report moderate functional interference, while some have extreme impairment to the point of dropping out of school or being unable to work.^{8,11-13} For instance, in a study exploring occupational functioning in 141 adults with BDD, 38% were currently unemployed, 72% had avoided going to work or school for more than one consecutive week, and 93% reported work or academic impairment because of BDD.¹³ Patients with BDD have also been shown to more often living alone, and are less likely to be married, compared to individuals without BDD.¹⁴

BDD usually begins during adolescence with a reported mean age at onset of 16.^{8,15,16} Moreover, individuals that have an onset before the age of 17 typically have a gradual increase of symptoms before onset, higher rates of attempted suicide, and more psychiatric comorbidity compared to individuals with a later onset.¹⁶ The literature also suggests that a greater proportion of females may have an early onset compared to males, but the evidence is inconclusive.¹⁶ The course of BDD is usually chronic if left untreated, with a low probability of full or partial remission, and a higher risk of partial or full relapse in those with an early age of onset.^{17,18}

1.2 PREVALENCE

Research has shown that approximately 2% of the population suffers from BDD. Specifically, the prevalence has been estimated to 0.7% in Italy,¹⁹ 0.8-2.4% in the US,^{20,21} 2.1% in Sweden,²² and 1.7-2.9% in Germany.²³⁻²⁵ The pooled, and weighted prevalence of the seven studies ($n=13,773$) is 1.9%, with BDD being slightly more common in females (2.1%), than in males (1.6%).²⁶

Until now, only two studies have estimated the prevalence of BDD in young people. In an Australian study of 3,149 adolescents (ages 12-18) the prevalence of BDD was estimated to 1.7%, with a higher prevalence observed in in ages 15-18, compared to ages 12-14 (2.4 vs. 1.1%).²⁷ Furthermore, no sex difference was found in the prevalence of BDD.²⁷ In contrast, a study from the US ($n=566$, ages 14-19) found a significantly higher prevalence in girls (2.8%), than in boys (1.7%), with the combined prevalence in boys and girls estimated to be 2.2%.²⁸

1.3 PSYCHIATRIC COMORBIDITY

The most common comorbidity in individuals with BDD is major depression, with lifetime rates between 72-78%.^{8,15} In clinically ascertained samples of BDD, 8-54% have also been diagnosed with a current depressive episode.^{11,14,15} On average, BDD precedes the onset of depression by two years,¹⁵ and the clinical experience is that patients in most cases report that it is their BDD that is causing the low mood. Social anxiety disorder (SAD), and obsessive-

compulsive disorder (OCD) has also shown high lifetime rates and frequently co-exist in patients diagnosed with BDD.^{8,14,15} Furthermore, the lifetime rates of alcohol use disorder (AUD) are high in BDD (19-39%), with a significantly higher lifetime rate of suicide attempts in BDD sufferers with a history of alcohol abuse, compared to those without.^{29,30}

Only two studies have explored associated psychopathology in adolescents with BDD. In one of the studies consisting of 33 adolescents (mean age 14.9 years), the lifetime prevalence of SAD, OCD, and AUD were 73%, 30%, and 3%, respectively.³¹ Findings from the other study that compared comorbid disorders in adolescents ($n=36$, mean age 17.8 years) to adults ($n=164$) concluded that the prevalence of lifetime major depression (81 vs. 73%), SAD (39 vs. 38%), OCD (28 vs. 34%), or AUD (31 vs. 45%) did not significantly differ between adolescents and adults.³² However, adolescents were significantly more likely to have higher rates of lifetime suicide attempts compared to adults.³² With only two published studies, more research is definitely warranted on the clinical correlates and pattern of comorbidities in adolescents, as it may have nosological as well as clinical implications for prognosis and treatment of BDD in young people.

1.4 ETIOLOGY

Family studies have found that 6-8% of individuals with BDD have a first-degree relative (i.e., a parent, full siblings or offspring) with a lifetime diagnosis of BDD, suggesting familial transmission of BDD.^{32,33} Despite scant research, recent twin studies have started to unravel the genetic and environmental influences that contribute to dysmorphic concerns.³⁴⁻³⁶ In principle, twin studies estimate the heritability (how much of the variation in a trait that can be explained by genetic factors), shared environmental factors (how much how much of the variation in a trait that can be explained by events that happen to both twins living in the same family), and non-shared environmental factors (how much of the variation in a trait that can be explained by events unique to a twin) for a certain trait. In a study consisting of 3,544 adult female twins with a mean age of 54.5, the heritability of dysmorphic concerns was estimated to be 44%, with non-shared environmental factors accounting for the remaining variance.³⁴ Similar results was found in another twin study consisting of adult twins of both sexes ($n=2,495$, mean age 34.5) where the heritability was estimated to be 42%, also with the remaining variance explained by non-shared environmental factors.³⁵ Additionally, evidence suggest that BDD shares a common genetic etiology with OCD and hoarding disorder (HD). However, genetic influences specific to BDD were also evident with environmental influences being largely disorder specific.³⁶ That is, genetic, as opposed to environmental influences are likely to account for the similarities across these conditions. Since previous twin studies have only included adult twins, the genetic and environmental influences on dysmorphic concerns in young people remains unknown.

As shown in the aforementioned twin studies, a large proportion of the explained variance for dysmorphic concerns is accounted for by environmental factors (56-58%). Some evidence suggests that childhood trauma and abuse may be associated with BDD. One study compared the rates of abuse in BDD ($n=50$) and OCD ($n=50$) and found that 38% of BDD patients retrospectively reported some form of abuse during childhood, compared to 14% of OCD patients.³⁷ Furthermore, in a study where 75 individuals with BDD completed the Childhood trauma questionnaire,³⁸ it was found that 79% retrospectively reported a history of childhood maltreatment, specifically, 56% reported emotional abuse, 35% physical abuse, and 28% sexual abuse.³⁹ There may also be an association between appearance-related teasing and BDD, as individuals with BDD report significantly more appearance-related teasing compared to healthy controls.⁴⁰ However, no environmental risk factors for BDD have yet to be identified by using research designs that also can control for environmental and genetic confounding.

1.5 TREATMENT

Because most people with BDD think that their problem has a physical basis, it is common for these individuals to seek out and receive cosmetic surgery or dermatological treatment.⁴¹⁻⁴³ However, such interventions seldom work, and may lead to a deterioration of the BDD symptoms.⁴³ Evidence based treatment for BDD consists of pharmacotherapy with selective serotonin-reuptake inhibitors (SSRIs) or cognitive behavioural therapy (CBT),⁴⁴ and guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend that patients with BDD should be offered either an SSRI or CBT (including exposure with response prevention).⁴⁵

1.5.1 Pharmacological treatment

Only two double-blind, placebo-controlled trials have been conducted in BDD. In the first trial, 34 participants received fluoxetine for 12 weeks after which 53% were classified as responders (defined as a 30% reduction in symptoms), compared to 18% in the placebo group.⁴⁶ In the second trial, 100 participants received open-label escitalopram for 14 weeks after which 58 responders were randomized to conditions in which they either continued escitalopram for six months or discontinued and switched to placebo for six months.⁴⁷ In the open label phase of the study, 67% of participants were classified as responders, and 20% achieved remission. Participants that stayed on escitalopram for another six months had fewer relapses compared to participants that were switched to placebo.

1.5.2 Psychological treatment

The first-ever RCT of CBT for BDD was conducted in 1995 and included 54 women that were randomized to either eight weeks of group therapy or no treatment.⁴⁸ Eighty-two percent of those that received CBT were in remission after treatment, which by all means is an impressive number. However, participants in this sample may not have been representative of the typical BDD patient in that roughly 40% of them reported *only* concerns with body weight. Shortly after, Veale and colleagues⁴⁹ published a small pilot RCT consisting of 19 participants randomized to either CBT or wait-list. On average, participants made a 50% reduction in symptoms after 12 sessions of individual CBT. Even though preliminary results suggested that CBT for BDD was promising, it would take almost two decades until the next RCT was published.

To date, the evidence base for specialized CBT that addresses the key features of BDD has grown. In total, six RCTs that have shown superiority of CBT compared to wait-list or active control.⁴⁸⁻⁵³ The recently published RCTs show response rates ranging between 52-81%, and a lasting effect on symptom reduction in the short term, and in a systematic review and meta-analysis consisting of all of the published RCTs it was established that CBT is an efficacious treatment for BDD.⁵⁴ Evidence from three naturalistic follow-up studies also suggest that participants who improve during the acute phase of CBT usually maintain these gains in the long-term (1-4 years after treatment).⁵⁵⁻⁵⁷

1.5.3 Treatment accessibility and barriers to treatment

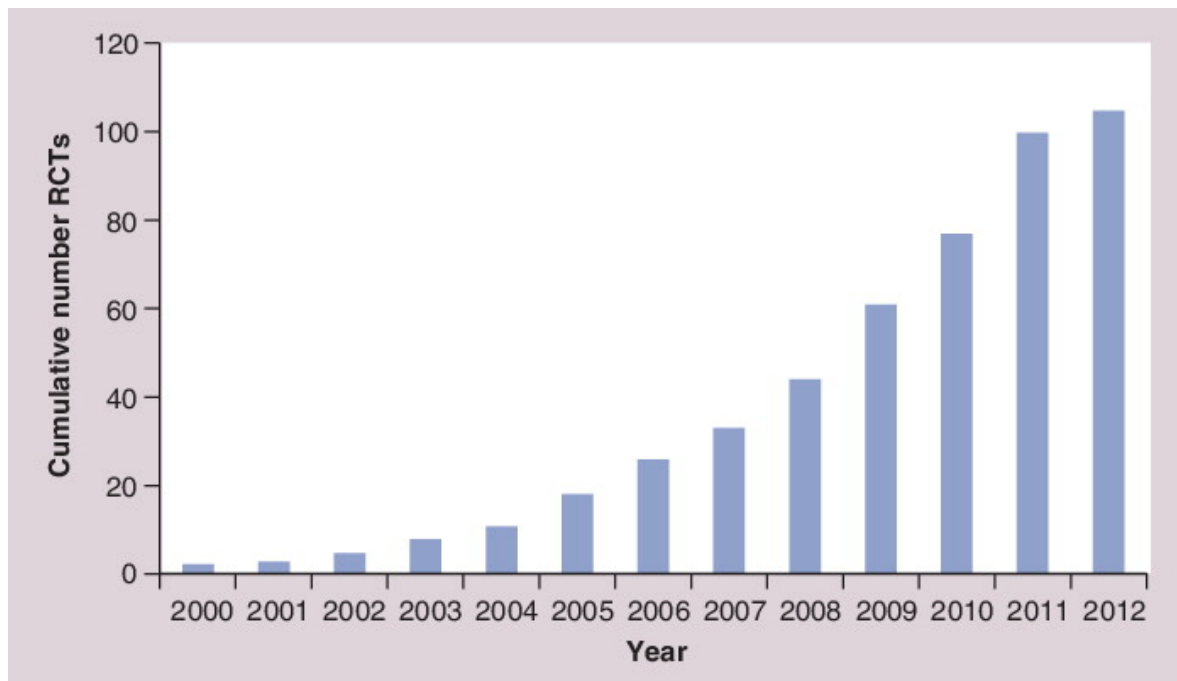
In an online survey from the US, 401 individuals with BDD answered questions about lifetime treatment use, 44% reported that they had received an SSRI and 66% reported that they had received psychosocial treatment for BDD; however, out of those only 17% reported that they specifically had received CBT.⁵⁸ In a similar study conducted in Germany (n=172), 19% of BDD sufferers reported that they currently were receiving pharmacological treatment, and 20% reported that they were receiving psychosocial treatment, out of which 10% specifically were receiving CBT.⁵⁹ These findings are corroborated in a prospective naturalistic 4-year follow-up study of 146 patients with BDD, where only 34% had received a course of an SSRI in a dose deemed adequate for treating BDD, and surprisingly few had received CBT (10%).¹⁸ For most people, barriers to treatment include a shortage of trained therapist that know how to provide specialized care,⁶⁰ underserved rural areas,^{61,62} as well as direct and indirect costs associated with treatment.⁶³ For BDD sufferers specifically, 33-50% report that they do not feel comfortable or are too ashamed to talk to a mental health professional about their appearance concerns as an important barrier for engaging in treatment.^{58,59}

The results from these studies are definitely a cause for concern. While effective treatment for this debilitating disorder does exist, the evidence only point in one direction, namely that most sufferers do not get access to it.^{17,18,58,59}

1.5.4 Internet based treatment

In response to the limited availability and accessibility of CBT, internet-based CBT (ICBT) has been extensively researched in the last decade with over 100 published RCTs for various health problems.⁶⁴⁻⁶⁷ In principle, there are two types of ICBT formats: with or without therapist support.⁶⁸ In the former, the patient, instead of going to a clinic, logs onto a secure website and works with written self-help materials and homework assignments while receiving support online from a clinician. Conceptually, the only difference between ICBT and conventional “face-to-face” CBT is in the mode of delivery. To illustrate, in conventional CBT the clinician provides step-by-step instructions on how to do behavioural changes. In ICBT, the patient gets the same instructions, but instead of a clinician providing them, the instructions are self-contained within the treatment platform as written self-help material. An important aspect of ICBT is that all patients receive exactly the same treatment, whereas in conventional CBT, therapist drift is common.⁶⁹ During the entire treatment, an identified clinician provides guidance by using the treatment platform’s built in message system. Patients can often send an unlimited number of messages to their clinician, and will usually receive a reply within 36 hours. The role of the clinician in ICBT is mainly to provide minimal support, troubleshoot, and coach the patient throughout the treatment.⁶⁸

Figure 1 | Cumulative number of published trials on Internet based CBT



Published in: Hedman H, Ljótsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. *Expert Review of Pharmacoeconomics & Outcomes Research* **2012**, 12, 745-764. Reprinted with permission from Taylor & Francis. (Copyright © 2012) Expert Review Ltd.

To sum up the evidence for ICBT, in a systematic review it was concluded that ICBT showed large treatment effects for conditions such as depression, anxiety, OCD, health anxiety, and irritable bowel syndrome, with small to moderate treatment effects for conditions such as chronic pain, reducing tobacco smoking, and stress.⁶⁵ Overall, if face-to-face CBT works, then ICBT works as well. Moreover, in a meta-analysis including 13 RCTs in which ICBT was directly compared with conventional CBT for social anxiety disorder, panic disorder, depressive symptoms, body dissatisfaction, tinnitus, male sexual dysfunction, and spider phobia, the pooled effect size did not differ significantly between the two treatment modalities.⁶⁶ This suggests that the treatments are equivalent, and that ICBT can be a compliment to conventional CBT. Additionally, ICBT has been successfully implemented in routine clinical care in Sweden for depression, social anxiety disorder, panic disorder, and irritable bowel syndrome.⁷⁰⁻⁷⁴ However, prior to this thesis, ICBT had not been tested for BDD.

1.6 AIMS OF THE THESIS

The first aim of the thesis was to develop and evaluate a novel internet based treatment for BDD, with the intention to increase availability and accessibility of CBT. The second aim was to conduct a genetic epidemiological study of BDD symptoms in adolescents and young adults. The questions that this thesis tries to answer are:

- Is ICBT a feasible and efficacious treatment for BDD in the short and long-term?
- What is the prevalence of BDD in adolescents and young adults?
- What causes dysmorphic concerns in adolescents and young adults?
- Is there an increased risk for co-existing psychopathology in adolescents and young adults with BDD?

Specific aims of each study are presented below.

Study I: The aim of Study I was to develop BDD-NET, a therapist supported ICBT program for BDD, and to test its feasibility.

Study II: The aim of Study II was to evaluate the efficacy of BDD-NET in a randomized controlled trial.

Study III: The aim of Study III was to determine the long-term treatment effects of BDD-NET and to explore the participant's reasons for partaking in the trial (same sample as in Study II).

Study IV: The aims of Study IV were to: [1] estimate the prevalence of BDD in three population-based, nation-wide twin cohorts (age 15, 18, and ages 20-28), [2] estimate the relative contribution of genetic and environmental influences on dysmorphic concerns, [3] estimate the risk for co-existing psychopathology in twins with BDD, compared to twins without BDD.

2 METHODS

2.1 DESIGN

Studies I-III were clinical trials conducted at the Department of Clinical Neuroscience, Centre for Psychiatry Research at Karolinska Institutet, and at Psychiatry Southwest, Karolinska University Hospital. Study IV was based on data derived from the Swedish Twin Registry,⁷⁵ including data from the Child and Adolescent Twin Study in Sweden (CATSS), and the Young Adult Twins in Sweden Study (YATSS).⁷⁶

Study I was an open pilot trial, evaluating the feasibility and efficacy of BDD-NET.

Study II was a single-blind parallel group superiority trial. Participants were randomized in a 1:1 ratio to either BDD-NET or online supportive therapy.

Study III was a naturalistic 2-year follow-up of all participants that had been treated with BDD-NET in study II.

Study IV utilizes both a descriptive, and an analytical epidemiological design. CATSS is a prospective longitudinal study of all twins born in Sweden since 1992, while YATSS includes all twins born in Sweden between 1985-1992. Prevalence of BDD symptoms and risk for co-existing psychopathology was estimated in CATSS when the twins were age 15 (CATSS-15), 18 (CATSS-18), and in ages 20-28 (YATSS 20-28). A classical twin design was used to determine the relative contribution of genetic and environmental influences on body dysmorphic concerns in these age groups.

2.2 PARTICIPANTS

Study I consisted of 23 self-referred participants with a diagnosis of DSM-5 BDD. Participants had first registered their interest in partaking in the trial on the study's secure web page (www.internetpsykiatri.se), where they also completed a battery of screening questionnaires. All participants underwent a formal structured psychiatric assessment by either a psychiatrist or a clinical psychologist working at a psychiatric unit specializing in obsessive-compulsive and related disorders. To establish a diagnosis of BDD, a semi-structured interview based on the structured clinical interview for DSM-IV axis I disorders (SCID-I) was used,⁷⁷ with an added question about repetitive behaviors to reflect the updates made to the diagnostic criteria of BDD in DSM-5. The presence of other psychiatric disorders was assessed with the mini-international neuropsychiatric interview (MINI).⁷⁸ Since internet based CBT for BDD had previously not been tested, only participants residing in proximity to the Karolinska University Hospital (i.e., Stockholm or Uppsala County) were eligible for inclusion in the trial due to safety reasons.

Study II included 94 self-referred participants with a diagnosis of DSM-5 BDD. In contrast to Study I, Study II included participants from all over Sweden. Participants had first registered on the study's web page where they completed a battery of questionnaires screening for BDD, alcohol or drug abuse and depression. Since Study II included participants from all over Sweden, in-person assessments at the Karolinska University Hospital were not possible. Instead, a formal structured psychiatric assessment was carried out over the telephone using the same semi-structured interviews as in Study I. Evidence suggests that the administration of structured psychiatric assessments over the telephone are as reliable as face-to-face interviews.⁷⁹

Inclusion criteria in Study I-II were:

- a primary diagnosis of DSM-5 BDD
- residing in Stockholm or Uppsala County (only in Study I)
- aged 18 or over
- score at least 20 (at least 16 in Study I) on the on Yale-Brown obsessive-compulsive scale modified for BDD (BDD-YBOCS).⁸⁰

Exclusion criteria in Study I-II were:

- changes in psychotropic drug treatment within two months prior to enrolment
- completed CBT for BDD within the past 12 months
- current substance dependence
- bipolar disorder or psychosis
- acute suicidal ideation
- a severe personality disorder that could jeopardize participation in treatment
- concurrent psychological treatment.

Study III included all participants that had received BDD-NET in Study II ($n=88$). All participants ($n=47$) that initially had been randomized to online supportive therapy were offered BDD-NET after the 3-month follow-up (6 months from baseline). Two participants were lost to follow-up, and four declined. In total, 41 of 47 participants accepted to crossover to BDD-NET, resulting in a final sample size of 88 participants that could be followed for up to 2-years after treatment to determine the long-term efficacy of BDD-NET.

Study IV included a total of 15,377 twins from the CATSS and YATSS cohorts that had available data from a validated screening tool for BDD. In CATSS, a total of 6,968 individual twins provided data when they were 15 years old, with a response rate of 53%. At the follow-up at age 18, 3,738 twins provided data (response rate=48%). In YATSS, 4,671 twins provided data with a response rate of 29%. The mean age in the YATSS cohort was 23.9 years ($SD=2.0$, range=20-28). Zygosity was determined by 49 single nucleotide polymorphisms.⁸¹ If DNA was not available, an algorithm based on twin similarities that correctly classifies 95% of twins compared to DNA testing was used.⁸²

Table 2 | Socio-demographic and clinical characteristics of participants

Variable		Study I (n=23)	Study II (n=94)
Sex	Female	16 (70%)	80 (85%)
	Male	7 (30%)	14 (15%)
Age	Mean age (SD)	30.3 (6.3)	32.6 (11.9)
	Range	22-49	18-72
Highest education	Primary school	n/a	10 (11%)
	High school	16 (70%)	54 (57%)
	College/university	7 (30%)	28 (30%)
	Doctorate	n/a	2 (2%)
Occupational status	Working	14 (61%)	53 (56%)
	Student	5 (22%)	23 (25%)
	Retired	n/a	3 (3%)
	Unemployed	4 (17%)	13 (14%)
	Disability pension	n/a	2 (2%)
Insight	Good or fair	10 (43%)	37 (39%)
	Poor	11 (48%)	43 (46%)
	Delusional	2 (9%)	14 (15%)
BDD duration	Mean length in years (SD)	15.3 (8.1)	19.0 (13.6)
Comorbidity	Current depressive episode	10 (43%)	51 (54%)
	Social anxiety disorder	5 (22%)	29 (31%)
	OCD	1 (4%)	18 (19%)
	Panic disorder	2 (9%)	11 (12%)
	Bulimia nervosa	2 (9%)	2 (4%)
	GAD	1 (4%)	2 (2%)
	ADHD	n/a	2 (2%)

SD=standard deviation; OCD=obsessive-compulsive disorder; GAD=generalized anxiety disorder; ADHD=attention deficit hyperactivity disorder; n/a=not applicable.

2.3 OUTCOMES

2.3.1 Study I-III

2.3.1.1 Primary outcome

The primary outcome in Study I-III was the BDD-YBOCS,^{80,83} which is considered the ‘gold standard’ for assessing BDD severity. BDD-YBOCS is a semi-structured clinician administered interview, consisting of 12-items assessing intrusive thoughts, repetitive behaviors, insight, and avoidance related to BDD. The total score ranges between 0-48, with higher scores indicating more severe symptoms. Treatment response was defined as at least a 30% decrease in the score of the BDD-YBOCS, which has shown to correspond well with at

least ‘much improved’ on the clinical global impression (CGI) – improvement scale.^{83,84} Remission was defined as no longer meeting diagnostic criteria for BDD. In Study I, the self-rated body dysmorphic dimensional scale (BDD-D)⁸⁵ was administered weekly during treatment. The BDD-D was used with the intention of tracking symptom change in individual patients as a proxy for treatment progression, however, the BDD-D was less than ideal in detecting minor changes in symptoms that may occur from week to week, and was therefore not included in Study II.

2.3.1.2 Secondary outcomes

Clinician-rated global functioning was assessed with the global assessment of functioning (GAF) scale.⁸⁶ Quality of life was assessed with the Body image quality of life inventory (BIQLI)⁸⁷ in Study I, and with EuroQol EQ5D⁸⁸ in Study II-III. The rationale for replacing BIQLI with the EQ5D in Study II-III was that EQ5D is commonly used to calculate quality-adjusted life years in health economic evaluations, both in Sweden and worldwide. Therefore, this choice allowed for future health economic evaluations of BDD-NET.

Depressive symptoms were assessed with the Montgomery-Åsberg depression rating scale self-report (MADRS-S),⁸⁹ which has a total score ranging from 0-54, with higher scores indicating more severe symptoms. MADRS-S was also used during treatment to be able to monitor fluctuations in mood, and suicidal ideation.

Treatment acceptability was assessed with a self-rated questionnaire where participants were asked if they were ‘very pleased’, ‘pleased’, ‘somewhat pleased’, ‘neither pleased nor displeased’, ‘somewhat displeased’, ‘displeased’ or ‘very displeased’ by the treatment provided in Study I and by the Client satisfactory questionnaire (CSQ)⁹⁰ in Study II. Treatment credibility, and expectancy of improvement was assessed with the C-scale.⁹¹ Adverse events were recorded with a self-report form in Study I-II.⁹²

2.3.2 Study IV

2.3.2.1 Dysmorphic concerns

In Study IV, the dysmorphic concerns questionnaire (DCQ)⁹³ was administered in the three population-based twin cohorts at age 15, 18, and ages 20-28. DCQ is a 7-item self-report questionnaire assessing degree of concern with one’s own physical appearance, with a total score ranging from 0-21. The DCQ has shown to be a reliable and valid measure of dysmorphic concerns in several studies, and discriminates BDD patients from clinical controls, for example patients diagnosed with an eating disorder or patients with disfiguring dermatological conditions.^{34,93-96} Several cut-offs have been recommended for the DCQ when screening for BDD, ranging between 9-17.^{34,95,96} In order to classify the most symptomatic cases, while also minimizing the number of false positives, the highest proposed cut-off

(DCQ ≥ 17) was used in Study IV. The DCQ was modified with an added instruction that responders should not include concerns related to weight when answering the questions. A supplementary question was also added: “Are your appearance concerns due to an injury or medical condition that has disfigured you or significantly changed your appearance?” Participants that provided clear and recognizable causes for disfigurement (such as amputation, cleft lip or scoliosis) were excluded from the analysis.

2.3.2.2 Co-existing psychopathology

Table 3 summarizes the instruments that were used to capture other psychiatric symptoms in the CATSS (age 15, and 18), and YATSS (ages 20-28) cohorts. Validated screening cut-offs were used to identify cases with probable attention deficit/hyperactivity disorder, autism spectrum disorder, obsessive-compulsive disorder, hoarding disorder, eating disorder, or alcohol abuse on the different instruments,⁹⁷⁻¹⁰⁴ except for self-reported lifetime anorexia nervosa or bulimia nervosa that were dichotomously scored (yes/no).

Table 3 | Instruments used in the different cohorts to capture co-existing psychopathology

Instrument	Cohort		
	CATSS-15	CATSS-18	YATSS 20-28
^a Autism-tics, ADHD and other co-morbidities inventory ⁹⁷	✓	✓	n/a
Obsessive-compulsive inventory revised (OCI-R) ¹⁰⁰	n/a	n/a	✓
Hoarding rating scale-self report (HRS-SR) ¹⁰⁵	✓	✓	✓
Eating disorder inventory-2 (EDI-2) ¹⁰⁶	✓	✓	n/a
‘Have you ever had bulimia nervosa/anorexia nervosa?’	n/a	n/a	✓
Alcohol use disorders identification test (AUDIT) ¹⁰⁴	n/a	✓	n/a

^a Parental interview when the twins were age 9/12; CATSS=Child and Adolescent Twin Study in Sweden; YATSS=Young Adult Twins in Sweden Study; n/a=not available.

2.4 INTERVENTIONS

BDD-NET consists of eight interactive modules that are delivered over 12 weeks through a tailored web platform using secure socket layering technology with 128-bit encryption to guarantee participant confidentiality. Each module is devoted to a certain theme and consists of self-help texts, worksheet exercises, and homework assignments.

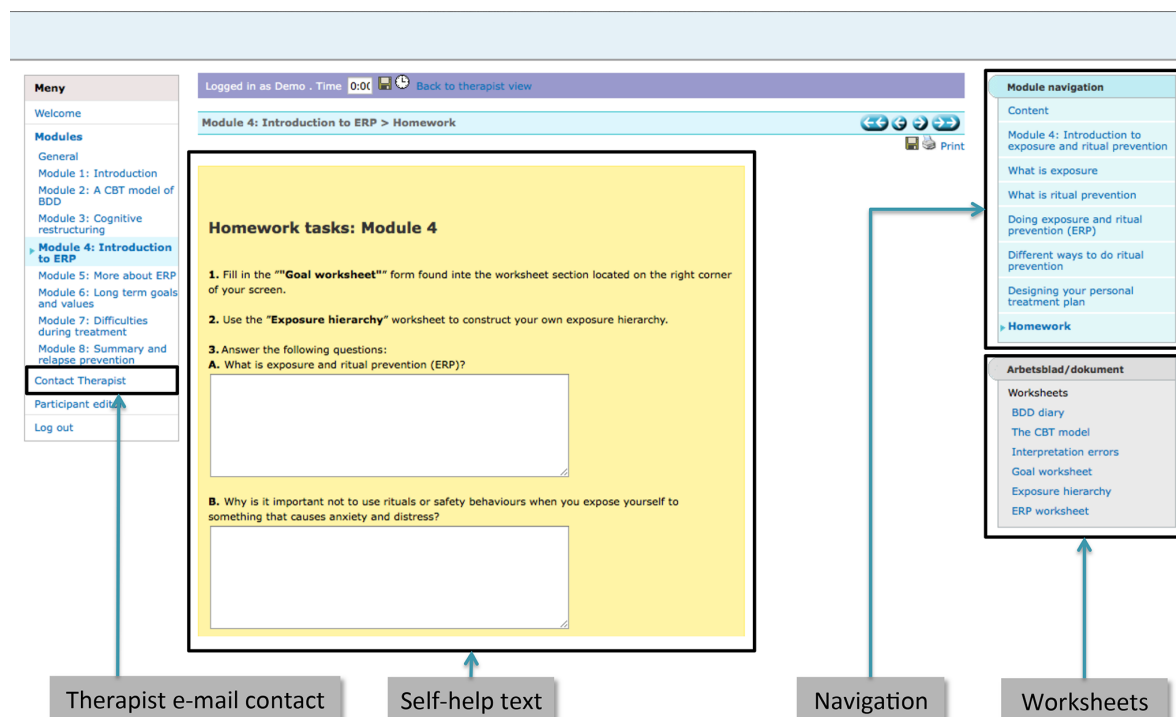
The treatment modules include a variety of strategies that work together to form a toolkit for overcoming BDD, and consist of:

1. **Psychoeducation about BDD:** Introduction to the treatment and information about BDD such as prevalence, etiology and common symptoms.
2. **A cognitive behavioural conceptualization:** A psychological explanation emphasizing the role of negatively reinforced avoidance and safety seeking behaviors as maintaining factors of BDD.
3. **Cognitive restructuring:** Participants evaluate negative thoughts and engage in cognitive restructuring.
4. **Introduction to exposure and response prevention (EX/RP):** An explanation of EX/RP. Participants set treatment goals and begin practicing in vivo EX/RP.
5. **More about exposure and response prevention:** Different aspects of EX/RP are highlighted and how to work with EX/RP over time.
6. **Valued directions and goals:** Participants identify values-based long-term goals within the domains of relationships, career and leisure activities.
7. **Difficulties during treatment:** Difficulties during treatment such as loss of motivation and problems in integrating exercises into everyday life are presented and discussed.
8. **Relapse prevention:** The participants summarize the main lessons learnt, what has been gained through the treatment and their future plans for treatment progress.

BDD-NET is therapist guided, but no face-to-face contact is provided. Instead, participants have unlimited access to an identified therapist by using the platforms built in message system. The role of the therapist is to coach the participant throughout the treatment, provide support, troubleshoot, and answer questions. Therapists also grant access to the next treatment module after it has been ensured that participants grasp the content of the current module, and are engaged in the assigned homework tasks. Therapists in Study I were two clinical psychologists with extensive experience in treating obsessive-compulsive and related disorders. Therapists in Study II were four clinical psychology students with no previous experience of treating BDD.

In Study II, the control condition consisted of online supportive therapy. Participants could talk freely about how BDD affected their everyday lives, and the therapists used skills drawn from counseling techniques, such as empathizing, minimal encouragers, reflecting, summarizing, and encouraging problem solving. In both treatment arms, participants were contacted at least once a week by their therapist (using the built in message system of the online platform). Participants in both arms could also send unlimited amounts of messages to their therapist and received a reply within 36 hours.

Figure 2 | Screenshot of the online platform



2.5 STATISTICAL ANALYSIS

2.5.1 Study I-III

All analyses were by intention-to-treat. Missing data in Study I-III were carefully examined and deemed to be missing at random. Patient characteristics were described by using the mean, median, range, and proportion for quantitative variables when appropriate.

In Study I, paired *t*-tests were used to determine if changes between baseline to post-treatment, baseline to follow-up, and post-treatment to follow-up were statistically significant. Fisher's exact test was used to explore if there was a significant association between the occurrence of an adverse event and responder status.

In Study II, linear mixed models with maximum likelihood estimations were used to estimate the effect of treatment group on the different outcomes across time.¹⁰⁷ The fixed effects of the models included indicator variables for time and treatment group, with an interaction effect of treatment group \times time to estimate the differential change between the two groups across time-points. Baseline scores of the BDD-YBOCS, MADRS-S, GAF, and EQ5D were included as covariates, with participant varying intercepts added as random effect in the models to account for idiosyncratic variation that is due to individual differences among participants.¹⁰⁷ Chi-squared tests were used for categorical data, and independent *t*-tests were used to test differences between groups when time was not a factor on the outcomes. Post hoc analysis of

participants in the control group that crossed over to BDD-NET after the controlled follow-up were carried out with paired *t*-tests.

In Study III, the effect of time on the different outcomes was estimated using linear mixed models.¹⁰⁷ The fixed effect included an indicator variable for time, with participant varying intercepts included as a random effect in the models. The dose-response of treatment was estimated by regressing the post-treatment BDD-YBOCS score on the number of completed modules, while controlling for the baseline BDD-YBOCS score.

In Study I, and III, missing data was imputed using multivariate imputation by chained equations.¹⁰⁸ Auxiliary variables that were correlated with missing data were included in the multiple imputations models to increase the precision of the estimates.¹⁰⁹ All estimates with standard errors were pooled from 50 (5 in Study I) imputations using ‘Rubin’s rules’,¹¹⁰ additionally, the small sample correction for pooled degrees of freedom was applied.¹¹¹ The use of multiple imputations to handle missing data has shown to perform well in data simulation models, even with 50% of missing observations.¹¹²

Effect sizes were calculated as Cohen’s *d*,¹¹³ and alpha was set at the standard 5%.

2.5.2 Study IV

Prevalence of BDD in the different cohorts was estimated both combined, and separately by sex, with the confidence intervals adjusted for the clustering of twins within families. The associations between BDD and co-existing psychopathology was examined using logistic regression models with a cluster robust sandwich estimator to account for the correlation of twins within twin pairs.¹¹⁴ Odds ratios were adjusted for zygosity, and age when appropriate. Few males screened positive for BDD. Consequently, the odds ratios could not be calculated for this group due to zero values. Therefore, risks for co-existing psychopathology are only presented in females that screened positive for BDD.

2.5.2.1 Classical twin model

The classical twin design makes it possible to estimate the relative contributions of genetic and environmental factors to the variation in a given phenotype. That is to say, a phenotype is a characteristic of an individual that can be observed, such as height, blood type, or a trait, and phenotypic variation refers to the variability of a certain phenotype that occurs in a population. For example, some people are tall while others are short, and some people worry a great deal about their appearance while others worry less or not at all.

The typical twin model decomposes the phenotypic variation into additive genetic effects (A), shared environmental effects (C), and non-shared or unique environmental effects (E). This is why the classical twin model is also called the ACE model in the literature.¹¹⁵ ‘A’ refers to the

heritability of the trait. In other words, this variable represents how much of the phenotypic variation that is due to additive genetic influences. 'C' constitutes how much of the variation that is due to shared environmental influences, or alternatively, the non-genetic factors that make twins reared together similar to one another, such as socioeconomic status or home environment. 'E' constitutes how much of the variation that is due non-shared environmental influences (and measurement error).¹¹⁶ Such factors may include differential peer influences, parental or teacher treatments and exposure to accidents.

The model assumes that: [1] people are as likely to choose partners who are similar for a certain trait as they are to choose partners who are different from themselves (random mating), [2] monozygotic twins share all of their co-segregating genes (they are genetically identical), [3] dizygotic twins share approximately half of their co-segregating genes (they are 50% genetically identical), [4] monozygotic and dizygotic twins do not differ in shared environmental influences (the equal environment assumption).¹¹⁵ This postulates that if there is a higher resemblance between monozygotic twins relative to dizygotic twins, it is solely due to genetic factors.

In twin modeling, intraclass correlations (ICCs) are estimated separately by zygosity, followed by model fitting analyses. The ICC coefficient range from 0 to 1, with 0 signifying no resemblance at all between twin pairs and 1 signifying perfect resemblance between twin pairs. Higher ICCs in monozygotic twins compared to dizygotic twins indicate that genetic factors influence the phenotype, while an ICC less than 1 in monozygotic twins indicate environmental influences.¹¹⁵ For example, if the variation in a given phenotype would only be caused by genetic factors, the monozygotic twin resemblance would be perfect ($ICC=1$) as they share all of their co-segregating genes, while dizygotic twins would have a 50% resemblance ($ICC=0.5$) because they only share half of their co-segregating genes. Simple estimates of the relative contributions of genetic and environmental influences to the variation of a given trait can be derived from the ICCs, but in order to construct confidence intervals around the estimates, adjust for the effects of covariates, or test hypothesis about the relative contribution of genetic and environmental influences on a trait, one must resort to model fitting implemented within the structural equation modeling framework.^{115,117}

In Study IV, ICCs were estimated for the DCQ total score in each age sample separately, followed by univariate maximum likelihood model fitting.¹¹⁵ All models were adjusted for sex differences in mean DCQ score, and additionally for age in YATSS 20-28. Ultimately, full ACE models were fitted in each age sample separately.

3 RESULTS

3.1 STUDY I – A PILOT TRIAL OF INTERNET BASED CBT FOR BDD

Study I included 23 participants diagnosed with BDD. Participants were assessed at baseline and then received 12 weeks of treatment. Post-assessments were carried out directly after treatment, and at three-month follow-up.

Large and significant reductions in BDD symptoms (assessed with the BDD-YBOCS) were observed at post-treatment. Further, but non-significant improvements were also observed on the BDD-YBOCS between post-treatment and the three-month follow-up. The within group effect size was large ($d=2.01$, 95% CI 1.05 -2.97). Participants also improved robustly on secondary outcomes of depression, quality of life and global functioning, with effect sizes ranging from moderate to large ($d=0.55$ -1.82). In total, 82% were classified as responders (at least a 30% decrease in BDD-YBOCS score).

Participants completed on average five of the eight modules, with most participants reporting that they spent between 2-7 hours per week working with the treatment (such as doing in vivo exercises). Overall, participants deemed the treatment as acceptable, with 85% reporting that they were pleased or very pleased with the treatment provided. Therapists spent on average 10 minutes per participant per week, reading and answering messages.

3.2 STUDY II – A SINGLE-BLIND RANDOMIZED CONTROLLED TRIAL

Study II included 94 participants diagnosed with BDD who were randomly allocated to either 12 weeks of BDD-NET ($n=47$) or 12 weeks of online supportive therapy ($n=47$). Participants were assessed at baseline, post-treatment (3 months from baseline), and 3-month follow-up (6 months from baseline) by blinded raters.

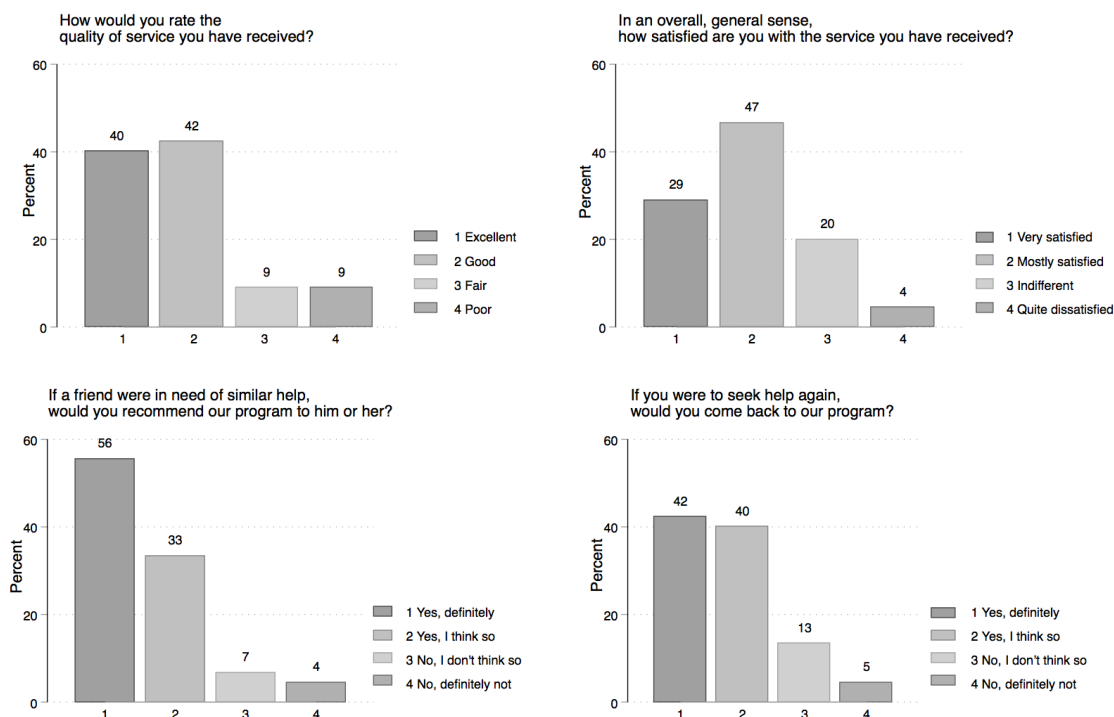
Participants in the BDD-NET group made significantly larger improvements on the BDD-YBOCS compared to participants treated with supportive therapy. The between group effect size was large ($d=.87$, 95% CI 1.05 -2.97). Additionally, the proportion of treatment responders was significantly higher for BDD-NET than supportive therapy (56 vs. 13%, $p<.001$), and at follow-up, 39% of participants in the BDD-NET group no longer met diagnostic criteria for BDD, compared to 9% in the supportive therapy group ($p<.001$). Furthermore, secondary outcome measures of depression, global functioning, and health related quality of life significantly improved in the BDD-NET group, but not in the supportive therapy group.

It was also found that there was a moderate correlation between change in BDD symptoms, and change in depressive symptoms ($r=.46$, $p<.001$), indicating that treatment tailored for BDD also had a subsequent effect on depression. At post-treatment, 56% of those meeting

diagnostic criteria for major depressive disorder at baseline were no longer depressed, and 47% were still in recovery from their depression at follow-up.

Overall, treatment acceptability was high, and 76% were very satisfied or mostly satisfied with the treatment provided. Moreover, 82% reported that they would recommend BDD-NET to a friend with similar problems.

Figure 3 | Treatment acceptability of BDD-NET



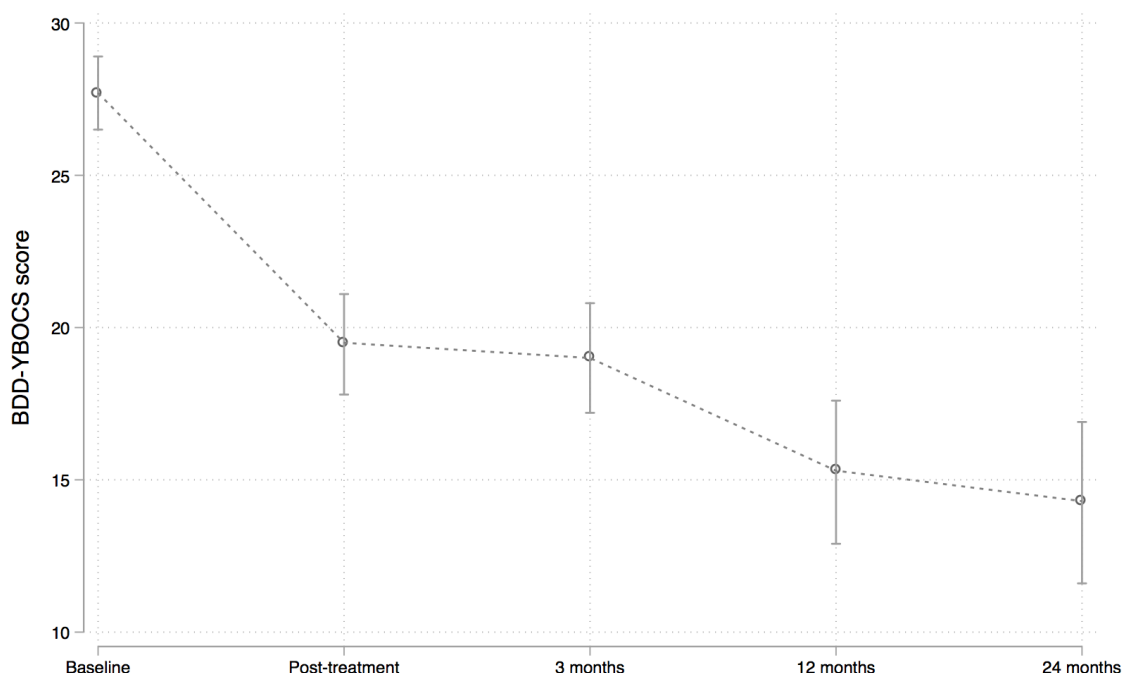
One third of participants experienced mild adverse events (such as increased anxiety, sleep disturbances or general negative wellbeing) during the first half of treatment, however, these symptoms had waned for most at the end of treatment. Experiencing an adverse event was not related to treatment response ($p=.34$). On average, participants completed six of the eight modules, and most considered BDD-NET to be acceptable. Therapist spent an average of 13 minutes per participant per week reading and answering messages.

All participants ($n=47$) who initially had been allocated to supportive therapy were offered BDD-NET after the 3-month follow-up (6 months from baseline). Two participants were lost to follow-up, and four declined. Participants ($n=41$) that crossed over to BDD-NET made significant improvements in primary and secondary outcomes after receiving 12 weeks of additional treatment with BDD-NET.

3.3 STUDY III – LONG-TERM EFFICACY OF INTERNET BASED CBT FOR BDD

Study III included all participants that had received BDD-NET in Study II. Participants that initially had been allocated to BDD-NET (n=47) were pooled with the participants that later accepted to cross over to BDD-NET (n=41). In total, 88 participants were followed for 2-years to determine the long-term treatment effects of BDD-NET.

Figure 4 | Effect of treatment over time on BDD-YBOCS



The efficacy of BDD-NET was sustained in the long-term, with further, and significant decreases observed on the BDD-YBOCS between the 3-month and 24-month follow-ups. The within group effect size from baseline to the 2-year follow-up was large ($d=1.79$ (95% CI 1.40-2.18)). It was also found that treatment adherence (defined as number of completed modules) had an impact on treatment outcome.

At 2-year follow-up, 69% (95% CI 57 to 80%) of participants were classified as responders and 56% (95% CI 43 to 69%) were in remission. Most participants that had responded to treatment maintained their responder status throughout the follow-up period, 29% had a delayed response to treatment, and 10% had relapsed. Additionally, secondary outcomes of depressive symptoms and global functioning were also sustained at the 24-month follow-up, but not health related quality of life measured with the EQ5D.⁸⁸

In conjunction with the 1-year follow-up, participants were briefly interviewed about their reasons for applying to the trial. In total, 63% reported that it was the possibility to do the treatment online that made them seek help for their BDD, 31% reported that they would have

sought care regardless, and 6% did not provide a clear answer. Additionally, 44% reported that it specifically was the possibility to do the treatment online, without having to meet with a clinician “face-to-face” as an important reason for engaging in treatment.

3.4 STUDY IV – GENETIC EPIDEMIOLOGICAL STUDY OF BDD

Study IV was based on two population-based nationwide twin cohorts, originating from the Swedish Twin Registry. Prevalence of clinically significant BDD symptoms, genetic and environmental influences on dysmorphic concerns, and risk for co-existing psychopathology was estimated in age 15 (CATSS-15; $n=6,968$), age 18 (CATSS-18; $n=3,738$), and ages 20-28 (YATSS 20 28; $n=4,671$).

3.4.1 Prevalence of BDD

The prevalence of twins that screened positive for BDD (a total score ≥ 17 on the DCQ) was 1% in age 15, 2% in age 18, and 1.1% in ages 20-28. Few males screened positive for BDD in age 15, however, the prevalence in males increased with age. Overall, the occurrence of BDD was significantly more likely in females than in males.

Table 5 | Prevalence of BDD in age 15, age 18, and ages 20-28

Prevalence, % (95% CI)	Cohort		
	CATSS-15 ($n=6,968$)	CATSS-18 ($n=3,738$)	YATSS ($n=4,671$)
Total	1.0 (0.8-1.3)	2.0 (1.6-2.6)	1.1 (0.8-1.4)
Male	0.2 (0.1-0.4)	0.4 (0.2-0.8)	0.6 (0.4-1.1)
Female	1.8 (1.4-2.3)	3.3 (2.5-4.2)	1.3 (1.0-1.8)

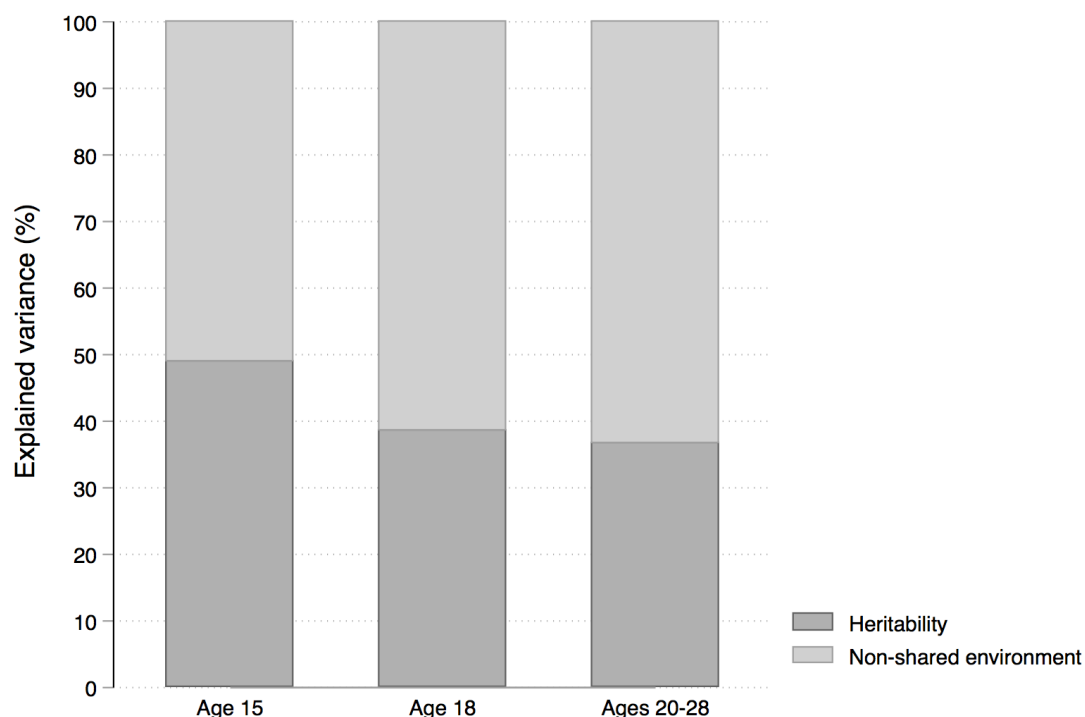
CI=Confidence interval; CATSS=Child And Adolescent Twin Study in Sweden; YATSS =Young Adult Twin Study in Sweden.

3.4.2 Genetic and environmental influences

In all cohorts, the ICCs were higher in monozygotic twins than for dizygotic twins, indicating genetic influences on dysmorphic concerns. However, ICCs in monozygotic twins were also lower than 1.0, indicating environmental influences on the phenotype. In the ACE-models, heritability was estimated to 49% (95% CI 38-54%) at age 15, 39% (95% CI 30-46%) at age 18, and 37% (95% CI 29-42%) in ages 20-28. Shared environmental factors were estimated at 0%

in all ages, with the remaining phenotypic variance explained by non-shared environmental factors estimated at 51% (95% CI 47-56%) in age 15, 61% (95% CI 54-68%) in age 18, and 63% (95% CI 58-69%) in ages 20-28.

Figure 5 | Genetic and environmental influences on dysmorphic concerns



3.4.3 Co-existing psychopathology

The number of males who screened positive for BDD was low, and as a result the odds ratios could not be calculated for this group due to zero values. Because of this, only results in females are presented. The risks for co-existing psychopathology in female twins that screened positive for BDD, compared to twins without BDD was elevated in all three age groups, with odds ratios (OR) ranging from 2.3-13.2. Some of the noteworthy findings are listed below.

- In age 15, the risk for attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) was increased.
- The risks for OCD and/or hoarding disorder (HD) were increased in age 18, and ages 20-28, but not in age 15.
- The risk for eating disorders symptomatology was increased in all ages, with the highest risk observed in age 15. There was an increased risk for lifetime bulimia nervosa in ages 20-28, but not for lifetime anorexia nervosa.
- In age 18, twins with BDD had a three times higher risk of harmful alcohol use compared to twins without BDD.

4 DISCUSSION

4.1 IS INTERNET BASED CBT EFFECTIVE IN TREATING BDD?

The short answer is yes. The pilot study of BDD-NET (Study I) showed preliminary promising effects, and most of the participants found the treatment provided as highly acceptable. These results were later confirmed in the RCT (Study II), showing that BDD-NET is an efficacious and safe treatment for BDD in the short-term. Furthermore, the follow-up study (Study III) showed that BDD-NET also is an efficacious treatment for BDD in the long-term. Most participants maintained their responder status at the 2-year follow-up, and very few of those that were classified as responders at post-treatment had deteriorated (10%). In total, 56% no longer met diagnostic criteria for BDD at the 2-year follow-up. Most participants in Study II found the treatment acceptable, and a vast majority of participants reported that they would recommend BDD-NET to a friend with similar problems. Moreover, in a recent systematic review and meta-analysis of CBT for BDD, the treatment effects of BDD-NET was shown to be in line with the treatment effects achieved in RCTs of conventional “face-to-face” CBT for BDD.⁵⁴

BDD-NET also had a positive effect on global functioning and depressive symptoms, and the improvements observed during the acute phase of treatment were sustained in the long-term, however, health related quality of life measured with the EQ5D was not. Specifically, health related quality of life was significantly improved from baseline to the 12-month follow-up. However, it had slightly decreased between the 12-month and 24-month follow-ups, and the improvements that had earlier been observed was no longer significant ($p=.06$). Since the EQ5D is primarily designed to assess quality of life in patients with somatic illnesses, it includes questions about mobility, pain, and self-care; none of which are usually impaired in BDD. Considering this, EQ5D may not be the best instrument for assessing quality of life in BDD; however, it is widely used in health economic evaluations to calculate quality-adjusted life years, allowing for future cost-effectiveness studies of BDD-NET.

4.1.1 Why do participants continue to improve after treatment?

A noteworthy observation is that participants continued to improve during the follow-up period and made further significant decreases in BDD symptom severity. We did not expect this; instead we had hypothesized that the treatment gains would remain stable from post-treatment throughout the follow-up period, as observed in the two recent follow-up studies of conventional CBT for BDD.^{56,57} During the follow-up period in Study III, 12 participants had received additional treatment (pharmacotherapy, CBT, or psychodynamic psychotherapy), however, they had on average higher BDD-YBOCS scores at the 2-year follow-up compared to those who had not received any additional care. Also, only four of the 12 participants that had received additional treatment were classified as responders at the 2-year follow-up. Thus,

the further improvements observed cannot solely be explained by additional treatment seeking among participants. Furthermore, there were about as many participants who had received additional treatment in our trial, as in the two recent follow-up studies of conventional CBT, where no significant improvements could be detected during the long-term follow-up.^{56,57} However, it should be noted that participants in the two recent RCTs, on average, had higher levels of depressive symptoms, were referred from primary or secondary care, and had worse insight, compared to our sample. Nonetheless, it is an intriguing finding that participants continued to improve after treatment.

The renowned psychologist Albert Bandura has described his theory of self-efficacy as,¹¹⁸ “...expectations of personal efficacy determine whether coping behavior will be initiated, how much effort will be expended, and how long it will be sustained in the face of obstacles and aversive experiences.” It could be speculated that the modality of treatment may have something to do with the additional improvements observed during the follow-up, that is; participants in BDD-NET may have developed a greater sense of self-efficacy than participants in conventional face-to-face CBT. In essence, BDD-NET is a guided self-help treatment, which implies that participants must take greater responsibility for learning the principles and methods of CBT and to apply these skills in their daily lives. Having to overcome obstacles on one’s own during treatment, without someone “holding their hand” may translate into an increased self-efficacy, which in turn may explain the further improvements observed during the follow-up period, perhaps as participants continued to employ the techniques that they had learned during the treatment in their daily lives.

4.1.2 Does ICBT reduce barriers to treatment engagement among individuals with BDD?

In Study III, participants were asked for their reasons for seeking participation in the trial. A majority reported that it was the possibility to do the treatment at home, without having to travel to a clinic that made them apply for participation. Outpatient health services are usually open during normal working hours, and CBT is often administered once a week, for several months. This service model disenfranchises individuals that may have difficulties in taking time of work or school.¹¹⁹ Additionally, some geographical areas are underserved and cannot provide CBT due to a lack of trained therapists.⁶⁰⁻⁶² Therapists in Study II were four clinical psychology students in their final year of training that had no previous experience of treating BDD. This shows that inexperienced therapists can guide participants throughout the treatment and still achieve favorable outcomes. BDD-NET clearly has the potential to increase accessibility and availability of CBT for BDD. It eliminates geographical barriers, and patients can work with the treatment at home, without having to travel to a clinic.

Furthermore, many individuals with BDD report that an important barrier to treatment engagement is that they do not feel comfortable or are too ashamed to talk to a health

professional about their appearance concerns.^{58,59} These previous findings are corroborated by the fact that many participants reported that an important reason for applying to the trial was the possibility to get treatment without having to meet with a clinician “face-to-face”. Thus, this type of treatment modality may lower the threshold for some people with BDD to engage in psychological treatment at all.

Some of the participants’ reasons for applying to the trial are quoted below:

- *“I would not have sought help at the health center. I’m was too ashamed that I worried so much [about my appearance]”*
- *“I have tried to get help for several years, but they [general practitioners or therapists] had no knowledge of BDD. I got no help, instead I was told that I look beautiful and shouldn’t worry about my appearance”*
- *“It felt safe to get help on the internet. I didn’t have to put up with a clinician staring at me...”*
- *“I would absolutely not have sought any other care. Do you expect me to book an appointment at the health center and say: help me, I feel ugly?”*

4.1.2.1 Limitations and methodological considerations of Study I-III

All participants were self-referred, indicating that they had some motivation to engage in psychological treatment for BDD, and about 40% had fair insight. There is some evidence suggesting that participants referred from mental health professionals have worse outcomes in internet based treatment, compared to participants that are self-referred or referred from general practitioners.¹²⁰ Therefore, the results may not be generalizable to all patients with BDD. However, 54 participants in Study II had had previous contact with secondary care, out of which 20 reported that the contact had been specifically because of their BDD.

Furthermore, the long-term follow-up in Study III was uncontrolled, and we cannot say for certain that it was participation in the trial that caused the further improvements observed. Participants were also asked about their reasons for applying to the trial at the 12-months follow-up, therefore, this may have introduced recall bias.

Attrition was generally low in Study I-II, however, in Study III, 36% of participants were lost to follow-up at the 2-year endpoint. In Study I and Study III, missing data was addressed by using multiple imputation.¹⁰⁸ In hindsight, using multiple imputations in Study I is clearly overkill, as only two participants were lost to follow-up. A better way to analyze the data in Study I would have been to use linear mixed models.¹⁰⁷ Because 36% of participants had missing data in Study III, multiple imputations was used to reduce bias and to improve parameter estimates.^{121,122} Compared to the complete-case analysis, the analysis using multiple imputations resulted in more conservative treatment effects. Nevertheless, the estimates in Study III should be interpreted with caution because of the large proportion of missing data.

4.2 WHAT IS THE PREVALENCE OF BDD IN ADOLESCENTS AND YOUNG ADULTS?

The prevalence of twins that screened positive for BDD was estimated to 1% in age 15, 2% in age 18, and 1.1% in ages 20-28. Our estimates of the occurrence of BDD in these nationwide population-based samples are also in line with the two previously published studies of BDD in adolescent high school samples, where the prevalence was estimated to be 1.7,²⁷ and 2.2%,²⁸ respectively.

In adults, BDD has shown to be slightly more common in females than in males (2.1% *vs.* 1.6%), whereas in our sample there was a significantly higher prevalence in girls than in boys, both in age 15 (1.8 *vs.* 0.2%), and in age 18 (3.3 *vs.* 0.4%). However, in ages 20-28, the difference had attenuated, and BDD was only slightly more common in females than in males (1.3 *vs.* 0.6%). These results indicate that there may be sex differences in the age at onset of BDD, and that an early age of onset of BDD is more common among adolescent girls.

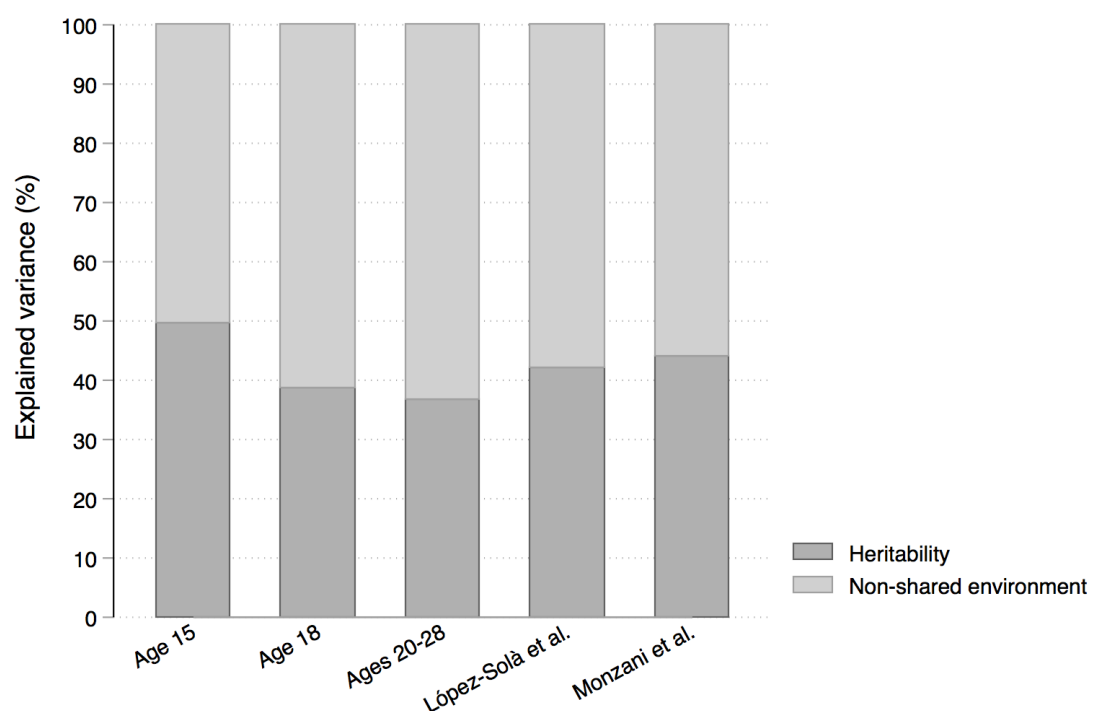
Additionally, sex difference in age of onset has been found in a sample of adults that participated in a prospective follow-up study of the course of BDD, in which 73% of those that reported an age of onset before the age of 18 were female.¹⁶ Furthermore, those with an early onset of BDD had significantly higher rates of attempted suicide, lifetime alcohol or substance abuse, lifetime eating disorders (bulimia nervosa or anorexia nervosa), and greater psychiatric comorbidity, compared to those with an onset after the age of 18.¹⁶ The aforementioned study also included a sample of BDD patients that were seeking psychiatric consultation or treatment for BDD, in which no sex difference in age at onset could be found, however, the discrepancy between the two samples may be explained by the fact that patients with suicidality, alcohol abuse or substance abuse were excluded in the latter sample. This may have introduced bias, as these comorbidities are more likely to occur in those with an early onset, who in turn, are more likely to be female. Clearly, age of onset in BDD warrants further investigation, as it may have important implications for the prognosis and treatment of BDD.

The estimated prevalence of 1-2% shows that BDD is relatively common in these age groups. However, BDD in adults has shown to be underdiagnosed, both in outpatient, and inpatient settings.¹²³⁻¹²⁶ Moreover, BDD in adolescents may be particularly underdiagnosed, as the symptoms may be mistaken for normal developmental concerns, and people with BDD are often reluctant to talk about their appearance concerns out of fear of being perceived as “vain”. Taken this into consideration, it makes it crucial that clinicians inquire directly about BDD symptoms in young people in order to be able to make the diagnosis.

4.3 WHAT CAUSES DYSMORPHIC CONCERNS IN ADOLESCENTS AND YOUNG ADULTS?

The classical twin study demonstrated that dysmorphic concerns had an estimated heritability between 37-49% in the different age groups, with the highest heritability estimated in age 15. Shared environmental influences were estimated to 0% in all ages, with the rest of the variance explained by non-shared environmental factors, estimated between 51-63%. These results are in line with the two previously published twin studies that estimated the heritability to 42% in twins with a mean age of 35, and to 44% in twins with a mean age of 55, with the rest of the variance also explained by non-shared environmental factors in both studies.^{34,35}

Figure 6 | Genetic and environmental influences on dysmorphic concerns across the lifespan



So what does this mean, and how can this information be used? First and foremost, the classical twin study tries to answer a commonly asked question: is dysmorphic concerns caused by nature or nurture? That is, why do some people worry a great deal about their appearance while other worries less or not at all, and how much of this variation is explained by genetic and environmental factors? The answer to that question is that heritability accounts for roughly half of the influence on dysmorphic concerns, with the rest of the variation explained by environmental factors unique to each twin. The classical twin study cannot inform us about which specific genes that contribute to the variation in dysmorphic concerns, nor does the estimates of environmental influences tell us what the specific exposures in the environment consist of that put an individual at risk of developing

dysmorphic concerns. However, the twin study does point us in the right direction of *where we should be looking* for the specific causes of dysmorphic concerns. Since roughly half of the variation is due to genetic factors, efforts to identify specific gene variants that constitute a risk factor for dysmorphic concerns are crucial, as identification of such genes may inform us about new pathways and potential targets for novel pharmacological interventions.

Historically, the identification of specific genes associated with psychiatric disorders has proven to be quite unsuccessful. In recent years, the candidate gene approach, where one or a few genes are studied at a time has been replaced by whole genome studies, where all (up to one million markers) common variation in the genome is studied at once. Such genome wide association studies (GWAS) have successfully identified genes related to schizophrenia,^{127,128} and depression.¹²⁹ For example, over 100 genetic variations that are associated with schizophrenia have been identified.^{127,128} The downside of GWAS is that due to the massive multiple tests done, sample sizes need to be very big, usually in the 5-digit range. At this time there is no published GWAS on BDD.

Furthermore, shared environmental influences were negligible across the three age groups, indicating that events of etiological importance is not due to effects that make twins reared in the same family similar (such as socioeconomic status, home environment, and neighborhood), instead, non-shared environmental influences accounted for the remaining variance; these could include environments such as differential peer influences, parental treatments, accidents, and other experiences outside of the family. At age 15, the relative contribution of genetic and environmental factors was equal, but by the time the twins had turned 18, the heritability had slightly decreased, with non-shared environmental factors accounting for a higher proportion of the variance in dysmorphic concerns. This may be explained by the fact that twin studies give a snapshot of the etiological influences in a population at a certain time. For instance, if the overall environment would be the same for everyone in a population, then the estimates of heritability may be high, as the only difference between individuals would be due to genetics, whereas in a population where the environment is more diverse between individuals, the estimates for heritability would decrease and the estimates for environmental influences increase. It could be speculated that, on average, the environment for 15-year olds differ from that of 18-year olds, which may in part explain why the environmental influences becomes more pronounced in age 18, compared to age 15. Since non-shared environment constitutes a large proportion of the variance overall, it is important to identify what these environmental exposures are. The literature on possible environmental risk factors in BDD is scarce, but some studies suggest that individuals with BDD, to a greater extent report childhood trauma and abuse,^{37,39} and more appearance related teasing compared to healthy controls.⁴⁰ However, future population-based researched is clearly needed to identify environmental risk factors that are associated with dysmorphic concerns.

4.4 IS THERE AN INCREASED RISK FOR CO-EXISTING PSYCHOPATHOLOGY IN ADOLESCENTS AND YOUNG ADULTS WITH BDD?

Compared to young people without BDD, adolescents and young adults that screened positive for BDD had elevated risks for co-existing psychopathology across all age groups. A noteworthy finding was that twins with BDD were twice as likely to screen positive for ADHD, and had a fivefold increased risk for ASD in age 15. The associations between BDD and these neuropsychiatric disorders have previously not been studied. However, some evidence suggests that executive functioning is impaired in BDD,¹³⁰ which also has been observed in children with ADHD and ASD.^{131,132} Additionally, ADHD and ASD have shown to be common comorbidities in children with OCD,¹³³⁻¹³⁵ and there is a genetic overlap between OCD and BDD.^{36,136} The increased risk for neuropsychiatric traits in adolescents with BDD is clearly an interesting finding that warrants further investigation in clinical samples.

The increased risk for HD in age 18, and OCD/HD in ages 20-28 gives support for the classification of BDD as an obsessive-compulsive and related disorder. Symptom-wise, HD and BDD do not seem to have much in common, (i.e., HD is characterized by a disability to discard possessions, resulting in obstructive cluttering of one's home). However, the reason these disorders co-exist may be hidden beneath the surface, as BDD shares a genetic overlap with the obsessive compulsive and related disorders, particularly OCD and HD.³⁶

BDD has mainly been nosologically linked to OCD,^{137,138} but it also shares similarities with the eating disorders.¹³⁹ Across the age groups, there was an increased risk for eating disorder symptomatology, and the self-reported lifetime occurrence of bulimia nervosa, and anorexia nervosa was 20% in ages 20-28, which is similar to the lifetime occurrence that has been reported in adults diagnosed with BDD.^{16,140} Although the risk for eating disorder symptomatology is increased, BDD may be underdiagnosed in patients with eating disorders. More specifically, in a study that screened 41 anorexia nervosa patients for BDD, 39% was diagnosed with comorbid BDD, and 94% reported that the onset of BDD had preceded the onset of anorexia nervosa; however, none of the patients had previously received a diagnosis of BDD according to their medical records.¹⁴¹ Moreover, anorexia nervosa patients with comorbid BDD had had higher rates of psychiatric hospitalization and three times the rate of suicide attempts, compared to anorexia nervosa patients without BDD.¹⁴¹ When considering the overall increase in risk for comorbid eating disorder symptomatology in adolescents and young people with BDD, patients with eating disorder symptoms should routinely be screened for symptoms of BDD, and vice versa.

Problematic drinking is common in BDD and the lifetime prevalence of an alcohol use disorder has been estimated to 20-43% in adults,^{8,15,29} and 3-31% in adolescents.^{31,32} In a study that inquired about the motives to drink alcohol among adults with BDD, a majority reported that BDD contributed to their alcohol use, and that they drank in order to cope with distress

due to their dysmorphic concerns.³⁰ More specifically, 50% reported that they drank because of distress due to dysmorphic concerns, 53% to forget about their dysmorphic concerns, and 59% reported that they drank to feel more at ease around others. Furthermore, drinking as a way to cope with negative affect in BDD was shown to be associated with higher lifetime rates of attempted suicide.³⁰

A worrisome finding in Study IV is that 43% of 18-year olds with BDD reported harmful or hazardous alcohol use, and that they were three times more likely to screen positive for alcohol misuse compared to adolescents without BDD. An important message to clinicians treating adolescents with BDD symptoms is to routinely screen them for alcohol misuse as the risk for problematic drinking is elevated in this population. Furthermore, these patients should be more carefully monitored for suicidal ideation, as drinking to cope with negative distress due to BDD is associated with increased rates of attempted suicide.

4.4.1.1 Limitations and methodological considerations of Study IV

The cut-off used on the DCQ to identify adolescents and young adults with a probable diagnosis of BDD had a sensitivity of 56% and specificity of 99%. We deliberately choose a high cut-off on the DCQ in order to minimize the number of false positives, while at the same time screening for the most symptomatic cases. With that said, we cannot be certain that all twins that screened positive for BDD would meet diagnostic criteria if assessed by a clinician. Moreover, response rates in CATSS-15, and CATSS-18 were adequate (response rates 48%-53%), however, in YATSS 20-28, the response rate was 29%. This may have affected the prevalence, and risk estimates, as it is possible that more symptomatic cases may be non-responders.

The classical twin design rests on certain assumptions, and should these be violated, it may bias the estimates of the genetic and environmental influences on a certain trait upwards or downwards. In the twin model, it is assumed that humans mate randomly, however, it has recently been shown that non-random mating may occur in psychiatric populations.¹⁴² If non-random mating would occur in individuals with dysmorphic concerns, the dizygotic twins would, on average, share more than 50% of their co-segregating genes, which in turn would lead to a deflation of the heritability estimates in the twin model.¹⁴³ Furthermore, it is assumed that the increased similarities in monozygotic twins compared to dizygotic twins are solely due to genetics, and that they are identical in their shared environmental influences (the equal environment assumption). Should this assumption be violated it would inflate the heritability estimates in the twin model.¹⁴³ However, it has been shown that the equal environment assumption is valid in the study of psychiatric disorders¹⁴⁴ and even if this assumption should be violated, the potential bias introduced is negligible.¹⁴³

4.5 FUTURE DIRECTIONS

The long-term efficacy of BDD-NET suggests that it could be disseminated to health services; however, several critical questions remain to be answered. First, because all participants were self-referred, it is unknown if the results are generalizable to patients seen in clinical settings. Second, although BDD-NET has shown equivalent treatment effects to conventional CBT in a meta-analysis, no direct comparison of the two treatment modalities have been made. Third, research on predictors and moderators of treatment outcome may guide clinicians in choosing the most suitable treatment from the start, avoiding unnecessary treatment failures. For instance, it could be that patients referred from secondary care may benefit more from conventional CBT, whereas the treatment effects for self-referred patients or patients referred from their general practitioner are similar between the two treatments. Fourth, as the cost of health care is globally increasing,¹⁴⁵ health economic evaluations of treatments used within the health care services are crucial, as decision makers operate within a limited budget. All these questions point in one direction. Namely that BDD-NET should be directly compared to conventional CBT in a non-inferiority trial that includes both self-referred patients, as well as patients referred from primary and secondary care. Such a study would allow for the determination of predictors and moderators of treatment outcome, as well as the cost-effectiveness of BDD-NET relative to conventional CBT.

Furthermore, the prevalence of BDD was relatively common in adolescents. This makes an adaptation of BDD-NET for this population warranted. Additionally, BDD-NET may prove especially useful for children and young people, as parents do not have to take time off from work to accompany their child to a pediatric psychiatry unit, and the child does not have to take time off from school to be able to get treatment.

In our nationwide population-based sample, there was a significantly higher proportion of girls that screened positive for BDD; however, the difference between the sexes was attenuated with advancing age. This may indicate that girls, on average, have an early age at onset of BDD, which should be investigated further. Moreover, the high risk for co-occurring eating disorder symptomatology and alcohol misuse among adolescent girls that screened positive for BDD could indicate shared genetic and/or environmental risk factors between these phenotypes. This finding clearly warrants further investigation, as it may have implications for our understanding of BDD in young people.

5 CONCLUSIONS

The aims of the thesis were to develop and evaluate a novel therapist guided, internet-based treatment for BDD (Study I-III) and to explore the prevalence of BDD, etiology of dysmorphic concerns, and co-existing psychopathology in adolescents and young adults (Study IV). To summarize, these studies showed that:

Internet based CBT for BDD is an efficacious treatment, both in the short-term and in the long-term, and the treatment effects are in line with those seen in conventional CBT for BDD. No serious adverse events occurred during treatment, and participants deemed the treatment as acceptable. The therapists providing support spent on average less than 15 minutes per participant per week. In principle, this enables a clinician to treat four times as many patients compared to conventional CBT. Since the treatment is delivered online, participants can work with the treatment from their homes, without having to travel to a clinic. Moreover, many participants reported that it was the possibility to do the therapy online as an important factor for engaging in treatment at all. Thus, internet based CBT has the potential to improve accessibility and availability of evidence based care for BDD when it is disseminated to health services.

In the nationwide population-based sample of adolescents and young adults (age 15, 18, and ages 20-28), 1-2% screened positive for BDD, showing that these symptoms are relatively common in young people. The occurrence of BDD was significantly higher in girls than in boys, but the prevalence in males became increasingly common with advancing age. This may indicate that there is a sex difference in the age at onset of BDD, and that females on average have an earlier onset than males. Across the age groups, genetic factors accounted for roughly half of the variation in dysmorphic concerns, with the remaining variation explained by non-shared environmental factors. Co-existing psychopathology was common in young people that screened positive for BDD, with some of the noteworthy findings listed below:

- At age 15, the risk for neuropsychiatric traits was increased.
- The risks for obsessive compulsive symptoms and/or hoarding symptoms were increased at age 18, and ages 20-28, but not at age 15.
- The risk for eating disorder symptomatology was increased in all ages, with the highest risk observed at age 15.
- In age 18, adolescents with BDD had a three times higher risk of harmful alcohol use compared to adolescents without BDD.

Hopefully, the findings in this thesis may lead to a better understanding of BDD, and help more people with this debilitating disorder to get access to evidence based care.

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Socrates, 411 B.C.

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